

### **Remarks**

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 are currently pending in the application. Claims 2, 9, 10, 12, 13, 21, 22, 24-48, 59 and 65-93 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claims 3, 11, 15, 23, 50, 58, 94-97, 99, 105 and 106 have been canceled in a previous reply. Claims 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 are presently canceled. Claim 1 is presently amended and support for the amendment is found throughout the present application, e.g., at page 15, line 23 through page 17, line 17 and the claims as-filed. These claims have been amended, withdrawn or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim withdrawn or cancelled for any reason.

By these remarks and amendments, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Applicants also wish to thank Examiner Chong for the courtesies extended to the Applicant's Representative and inventor Dr. Tully in the Personal Interview held July 30, 2009.

### **Claim Rejections under 35 U.S.C. § 103**

The Examiner has sustained the rejection of Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 under 35 U.S.C. § 103 as obvious over United States Patent Number 5,547,979 ("Christensen") in view of the Merck Manual. September 30, 2008, Office Action ("OA") at 3. According to the Examiner, Christensen teaches "the phosphodiesterase inhibitor[] rolipram . . . in a method of treating stroke in a human." *Id.* The Examiner also notes that: "The active ingredient may be administered from 1 to 6 times a day or as recognized by one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition, the form, route, site of administration, patient, and that such optimums can be determined by conventional techniques." *Id.* The Examiner further states that: "the limitations regarding 'which enhances CREB pathway function' and 'wherein rehabilitation of said cognitive deficit is effect by producing a long lasting performance gain' are given little patentable weight because these biological processes are inherent

when the same compound is administered in the same patient population at the same dosage.” *Id.* at 3-4.

The Examiner concedes that Christensen fails to disclose “multiple cognitive training sessions sufficient to produce an improvement in performance of a cognitive task whose deficit is associated with a central nervous system disorder.” OA at 4. However, the Examiner posits that this failing of Christensen is remedied by the Merck Manual. According to the Examiner, the Merck Manual teaches that “a training protocol should be started as early as possible towards a patient’s rehabilitation to stroke. Such rehabilitation includes encouragement, orientation toward the outside environment, eating, dressing, toilet functions, other basic needs, passive exercise, particularly of paralyzed limbs, and breathing exercises.” *Id.* The Examiner concludes that these rehabilitation techniques meet the limitation of cognitive training and also notes that “it is obvious to one of ordinary skill in the art to not stop at a single training session in the rehabilitation of a stroke victim since the process takes a great deal of time with many repeated sessions.” *Id.*

The Examiner continues that a person of ordinary skill in the art would have two reasons to combine the cited references: “(1) both Christensen and the Merck Manual disclose treatment for the same purpose, which is treating stroke patients and because (2) of the additive therapeutic effects of employing two methods of treating stroke simultaneously.” OA at 5. The Examiner concludes that it would have been obvious “to have combined the cognitive multiple training sessions, as described in the Merck Manual, before and during administration of the phosphodiesterase inhibitor, rolipram, in the method of treating stroke in a human, as disclosed by Christensen.” *Id.* Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish a *prima facie* case of obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant’s disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the

Examiner must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966). As a preliminary matter, and solely to advance prosecution of the application and not in acquiescence to the present rejection, Applicants currently cancel claims 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 without prejudice to or disclaimer of the subject matter defined therein.

Christensen does not teach or suggest the improvement in performance of a cognitive task following application of PDE4 inhibitors to treat stroke, as contended by the Examiner. Instead, Christensen relates to PDE4 inhibitors, such as rolipram, that inhibit the production of Tumor Necrosis Factor (TNF), which "has pro-inflammatory activities which together with its *early* production (during the *initial* stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock." Col. 6, ll. 20-25 (emphasis added). The only proper interpretation of this statement is that PDE4 inhibitors may inhibit the inflammatory response, thereby preventing further tissue damage often associated with inflammation during the immediate time period following a brain injury. Indeed, this portion of Christensen effectively teaches away from the repeated application of PDE4 inhibitors in conjunction with stroke, due to the *early* production of TNF during the *initial* stage of an inflammatory event.

Applicants established in their prior response that Christensen relates to the treating various "disease states mediated or exacerbated by TNF production." Christensen, Abstract. Indeed, Christensen's methods all focus on the administration of a "TNF inhibiting amount" of a compound. *See, e.g., id.* Col 2, ll. 10-20. Christensen therefore only relates to the use of the compounds for mediation of TNF exacerbated tissue injury (for example, after stroke) and does not teach or suggest the improvement in performance of a cognitive task following application of PDE4 inhibitors, much less

the repeated application of PDE4 inhibitors in conjunction with repeated cognitive training to produce a long-lasting performance gain, as claimed. The present rejection is exactly the same as the situation as admonished by the Supreme Court in *Graham*, where "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." 383 U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007). Christensen merely relates to use of rolipram for mediation of tissue injury exacerbated by TNF. The Merck Manual merely relates to the physical rehabilitation of stroke patients. Indeed, there nothing of record that the physical rehabilitation of stroke patients, as independently set forth in the Merck Manual, should be combined with Christensen's independent use of rolipram for mediation of tissue injury exacerbated by TNF.

Indeed, neither Christensen nor the Merck Manual, alone or in combination, teach or suggest the improvement in performance of a cognitive task following training in conjunction with the application of PDE4 inhibitors, both the training and application occurring after the acute phase of a stroke and during the rehabilitation phase of a stroke, as set forth in presently-amended independent claim 1, much less the repeated application of PDE4 inhibitors in conjunction with repeated cognitive training to produce a long-lasting performance gain relative to training alone, as claimed. These elements are individually and collectively absent from the prior art of record and the present rejection can only be a case of improper hindsight reasoning.

Additional evidence confirms this view and shows that one of ordinary skill in the art would not have had a reasonable expectation of success by combining the teachings of Christensen and the Merck Manual.

**1. Christensen Can Only be Read to Teach Administering the Inhibitor During the Acute Phase of Stroke**

The section in Christensen discussing stroke and TNF is limited to two sentences, indicating that TNF is a pro-inflammatory cytokine that appears to mediate tissue injury during the initial stages of inflammation following stroke-onset. Col. 6, ll. 20-25. This section also references *Munro et al.* (1989), a study of cytokine-mediated immune inflammation in a baboon skin model. *Munro et al.* (1989) Am. J. Path.

135:121-132.<sup>1</sup> *Munro et al.* indicates that a single injection of TNF leads to rapid expression of cellular adhesion molecules on endothelial cells, associated with infiltration of inflammatory leukocytes. *Id.* at 125, Fig. 2. These findings show a crucial role for TNF in the initial pathological response following stroke.

Directly supporting a central and early role for TNF in stroke pathology is extrinsic evidence from studies of stroke models. For example, *Barone et al.* (1999), authored by investigators at the same pharmaceutical company as the inventors of Christensen, summarizes studies showing rapid expression of TNF after stroke-onset, along with induction of cellular adhesion molecules on endothelial tissue that recruit inflammatory cells to the stroke site. *Barone et al.* (1999). *J. Cereb. Blood Flow Metab.* 19:819-834, \*7- \*10.<sup>2</sup> *See also Liu et al.* (1994) *Stroke* 25:1481-1488,<sup>3</sup> 1483 (TNF- $\alpha$  mRNA induction was observed in ischemic cortex as early as 1 hour after focal cerebral ischemia in mouse stroke model). These studies corroborate the teachings of *Munro et al.* that cytokine-activated endothelium plays an important and early role in the adhesion and subsequent accumulation of leukocytes following ischemia.

Together, these findings teach the skilled artisan that TNF is near the top of the inflammatory cascade, and once activated by stroke, triggers a set of downstream events that damage the brain during the acute phase of stroke. Indeed, statistical analysis of relevant animal studies shows that following stroke-onset, “irreversible focal injury begins within a few minutes and is complete within about 6 hours.” *Zivin* (1998) *Neurology* 50:599-603,<sup>4</sup> 599-601, including Figure.

Accordingly, one of ordinary skill in the art would view the therapeutic window for inhibiting TNF production as a necessarily narrow one, confined to a limited period shortly after the onset of stroke and hence would not attempt to treat stroke by inhibiting TNF production once the downstream pathology has been set in motion. This clear scientific evidence is in direct opposition to the Examiner’s contentions in the present rejection. Also directly supporting this view are studies with TNF inhibitors

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<sup>1</sup> This reference may be found in the Information Disclosure Statement submitted concurrently with this response (“IDS”).

<sup>2</sup> This reference may be found in the IDS; also available on-line:  
<http://www.nature.com/jcbfm/journal/v19/n8/abs/9590577a.html>

<sup>3</sup> This reference may be found in the IDS.

<sup>4</sup> This reference may be found in the IDS.

in various disease models, including stroke models. Christensen discloses experiments with TNF inhibitors in inflammatory models of endotoxin shock, relying on protocols described in *Hanna* WO 90/15534, Dec. 27, 1990 and *Badger et al.*, EPO Published Application 0 411 754, Feb. 6, 1991.<sup>5</sup> To the extent that these protocols disclose the actual timing of TNF inhibitor administration, they all are based on a single injection of inhibitor administered **before** the inflammatory reaction is induced. *See, e.g., Hanna*, Figs. 1 and 4; *Badger et al.*, Figs. 1 and 3.

Similarly, studies on stroke models themselves have invariably relied on administering TNF inhibitors either before stroke or shortly after stroke-onset. *See, e.g., Meistrell et al.* (1997) *Shock* 8:341-348,<sup>6</sup> 344-345 (showing a clinically relevant window for antibodies and inhibitors against TNF for up to 2 hours after focal ischemia in rat); *Nawashiro et al.* (1997) *J. Cereb. Blood Flow Metab.* 17:483-490,<sup>7</sup> \*3-\*4 (intracranial administration of TNF binding protein conferred long-term protection when administered up to one hour post cerebral occlusion);

These studies all teach one of ordinary skill in the art to consider only a narrow time window, during the acute phase of stroke, when considering the use of inhibitors to treat stroke pathology. Indeed, the skilled artisan would also know that the only approved drug for treating acute ischemic stroke is tissue plasminogen activator, which offers no therapeutic utility beyond a 3-hour window after stroke onset. *See, e.g., Hickenbottom et al.* (2000) *Neurol. Clin.* 2:379-397,<sup>8</sup> 384 (Eligibility criteria for treatment of ischemic stroke with tPA requires clear symptom onset within 3 hours.) The Merck Manual (16<sup>th</sup> ed., 1992), which was cited by Examiner in the OA at pages 4-5, is also consistent with this view: its discussion of “immediate care” treatment considers the possibility of various medical and surgical interventions, among them “clot lysing agents, including tissue plasminogen . . . in the very early treatment of acute stroke,” concluding with the following guidance: “To be effective, treatments to minimize brain damage from acute stroke **have to begin very soon after stroke onset**” (emphasis added). Merck Manual at 1455.

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<sup>5</sup> Each of these references may be found in the IDS.

<sup>6</sup> This reference may be found in the IDS.

<sup>7</sup> This reference may be found in the IDS.

<sup>8</sup> This reference may be found in the IDS.

In sum, the underlying biology of TNF in early stroke pathology, coupled with the recognized narrow therapeutic window for treating acute stroke, corroborates Applicant's contention that one of ordinary skill in the art would only read Christensen to administer a TNF inhibitor, including rolipram, during the acute phase of stroke.

**2. One of Ordinary Skill in the Art Would Have no Reasonable Expectation of Success by Combining the Teachings of Christensen with Cognitive Training During Rehabilitation.**

As discussed above, the prior art consistently teaches a detrimental role for TNF in the early stages of stroke, mirrored by the success of early therapeutic interventions based on TNF inhibitors. In addition to this knowledge, however, one of ordinary skill in the art would also be aware of studies pointing to a **beneficial** role for brain inflammation (and TNF) in post-injury processes. *See, e.g., Rothwell et al. (1996) Nature Med 2:746-747*<sup>9</sup> (discussing the complexities of TNF signaling in the brain, including evidence strongly suggesting a role in protecting neurons after cerebral stroke); *Liu et al. at 1483* (late expression of TNF- $\alpha$  in macrophages 5 days after focal cerebral ischemia implicated in resolution of ischemic brain injury).

These studies underscore the dynamic changes that occur in the brain following stroke, reflecting a progression of events from repair and remodeling to neuronal plasticity and recovery of function. Accordingly, these studies teach to one of ordinary skill in the art that inflammatory mediators, including TNF, have dual roles in the period following stroke, with detrimental effects during the acute phase and beneficial effects during the post-injury recovery phase. *See e.g., Barone et al.,\*16, Fig. 6* (describing the “‘yin/yang’ involvement of brain inflammation in the exacerbation and evolution of initial ischemic injury, and in the repair and recovery of function of neuron tissue following injury.”); *Shohami et al. (1999) Cytokine and Growth Factor Reviews 10:119-130*<sup>10</sup> (discussing deleterious consequences of acute TNF- $\alpha$  response in injured brain in view of reports on the beneficial effects of TNF- $\alpha$  from in vitro studies or knockout mice).

These reports clearly teach away from anti-inflammatory interventions during the post injury phase of stroke. Applicants note that this phase encompasses processes

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<sup>9</sup> This reference may be found in the IDS.

<sup>10</sup> This reference may be found in the IDS.

such as neural plasticity and functional recovery that underlie the cognitive training protocols claimed in the instant application. Accordingly, one of ordinary skill in the art would have no reasonable expectation of success by simultaneously combining the inhibitor treatment methods of Christensen with the rehabilitative interventions in the Merck Manual. This scientific evidence further undermines the Examiner's unsupported position that motivation exists to combine different methods of stroke treatment based on "the additive therapeutic effects of employing two methods of treating stroke simultaneously." OA at p. 5.

**3. The Merck Manual Can Only Be Read to Teach Cognitive Training After the Acute Phase of a Stroke**

The Merck Manual reference used by the Examiner was cited as "extrinsic evidence of the ordinary protocol in treating a stroke patient." March 5, 2004, Office Action at page 2. A proper reading of this reference shows that cognitive training is only administered after the acute phase of stroke. The specific topic of "Treatment" in the Merck Manual is divided into two phases: "Immediate Care" and "Rehabilitation and Aftercare," which are discussed in separate and sequential sections. Merck Manual at 1455-1456.

The Immediate Care section is directed to treating and stabilizing a stroke patient during the acute phase. Medical care focuses only on procedures that target stroke pathology directly, such as the immediate use of agents to dissolve clots. Merck Manual at 1455. Physical manipulations focus only on passive procedures: "Passive exercise, particularly of paralyzed limbs, and breathing exercises, if possible, should be started early."<sup>11</sup> *Id.*

In contrast, the Rehabilitation and aftercare section is directed to designing and implementing a remedial program for the stroke patient after the acute phase has ended. The "design of a remedial program" is promoted though "early, repeated appraisals of the patient's status by physician, physiotherapist, and nursing staff." Merck Manual at 1455. Medical care during remediation focuses only on managing secondary issues, if

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<sup>11</sup> This quote was originally cited during prosecution as evidence that "a training protocol should be started as early as possible towards a patients [sic] rehabilitation." But as discussed here, such passive procedures are part of acute stroke care and completely distinct from cognitive training protocols, which are active interventions administered during post-stroke rehabilitation.



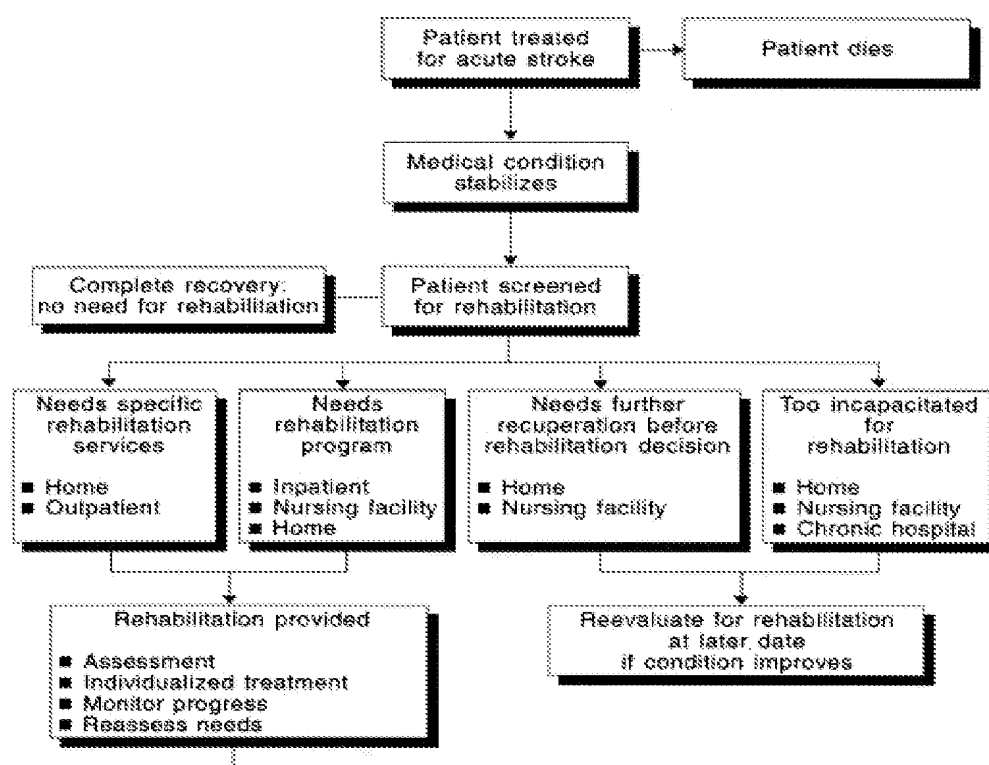
they arise, such as anxiety and depression. *Id.* Only this section discusses physical manipulations that are **active** procedures, including “occupational and physical therapy.” *Id.* at 1456. Early medical care during remediation also includes procedures to develop the patient’s strength and alertness. *Id.*

In other words, the Merck Manual teaches one of ordinary skill in the art that active training procedures, including cognitive training, only begin after acute medical treatment of the patient (which may include passive interventions) and even then, only after the patient has been assessed and a remedial program designed. These teachings also underscore the distinct boundary between treatments that target stroke pathology directly, which occur during the acute phase, and cognitive training protocols that target lasting cognitive impairment in appropriately screened patients during the rehabilitation phase.

Other extrinsic evidence provides a more comprehensive view of rehabilitation that fully corroborates and expands upon the full teachings of the Merck Manual, and contradicts the Examiner’s unsupported conclusions. One authoritative source of such evidence is the 1995 Clinical Guideline by the Department of Health and Human Services on Post-Stroke Rehabilitation. (“*Guideline*”)<sup>12</sup> As noted in the introduction, “this guideline was written by an independent multidisciplinary panel of private-sector clinicians and other experts,” “employed explicit, science-based methods and expert clinical judgment,” and “reflects the state of knowledge, current at the time of publication, on effective and appropriate care.” Figure 2 from the *Guideline* shows a “Clinical Flow Diagram for stroke rehabilitation”:

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<sup>12</sup> This reference may be found in the IDS; also available on line at [www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.27305](http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.27305)



This diagram graphically depicts the teachings of the Merck Manual. Rehabilitation, as the term is used in the instant application, does not occur until the acute stroke phase has ended and the patient's medical condition has stabilized – and even then, not until the patient has been screened for rehabilitation and assessed to develop an individualized treatment plan.

As extensively discussed in the *Guideline*, such treatment can target a broad array of impairments, including those impacting cognition and motor function. Table 12, for example, provides guidance regarding the assessment stage of a rehabilitation program: “Impairment measures (Individualized to patient's deficits)” cover a wide range of neurological deficits, including motor function, language and speech, and disabilities – deficits that are amenable to treatment by the cognitive training methods disclosed in the instant application. Similarly, the *Guideline* evidences the effectiveness of biofeedback (Table 16), as well as the effectiveness of rehabilitation treatment for motor deficits (e.g. Table 21), for cognitive and perceptual deficits (Table 22), and speech and for language deficits (Table 24).

Also consistent with the Merck Manual is the clear distinction in the *Guideline* between acute stroke interventions and stroke rehabilitation treatments. Acute stroke

interventions are designed “to facilitate recovery and present complications” and the “[h]ighest priorities are to prevent recurrent stroke, prevent complications, ensure proper management of general health functions, mobilize the patient, and encourage resumption of self-care activities as soon as medically feasible.” *See Guideline*, Chapter 4, Rehabilitation During Acute Care for Stroke.

In contrast, rehabilitation treatments “aim to reduce impairments (remediation) or to help patients relearn old skills or develop new ones despite persisting neurological deficits (compensation). . . Rehabilitation is done *with* the patient rather than *to* the patient.” *See Guideline*, Chapter 6, “Principles of Rehabilitation. This view of rehabilitation as an active intervention agrees with the Merck Manual.

This view of rehabilitation treatment is consistent with disclosures in the present application, for example the teaching that “[c]ognitive training protocols (e.g., physical therapy, bio-feedback methods) are employed in rehabilitating stroke patients (stroke rehabilitation), particularly rehabilitating impaired or lost sensory-motor function(s).” U.S. Pat. App. Ser. No. 09/927,914 at page 3, ll. 23-25.

It is also consistent the stroke references incorporated in the specification. For example, the following Table summarizes the cognitive training protocols in the stroke-related references cited in the instant application.

#### Stroke References Incorporated in the Present Application

Citation	Time of Stroke-Onset
<i>Dean et al.</i> (2000) Task- related circuit training improves performance of locomotor tasks in chronic stroke: a randomized, controlled pilot trial. Arch. Phys. Med. Rehabil. 81: 409-17.	Subjects were at least 3 months post-stroke.
<i>Greener et al.</i> (1999) Speech and language therapy for aphasia following stroke. Cochrane Database of Systematic Reviews 1999, Issue 4. Pgs. 22-32.	Interval times (for multiple studies) ranged from at least 2 weeks to more than 6 months after stroke-onset.
<i>Johansson B.</i> (2000) Brain plasticity and stroke recovery: the Willis lecture. Stroke 31: 223-230; 226.	Does not discuss specific studies, apart from a brief mention of report that “changes in activation pattern can be induced by forced training of the paretic hand even 4 to 15 years after stroke onset.”
<i>Lange et al.</i> (2000) Organizational strategy influence on visual memory performance after stroke: cortical/subcortical and left/right hemisphere contrasts. Arch. Phys. Med. Rehabil. 81: 89-94.	“On the average, the neuropsychologic test battery was administered 39 days post-onset”.
<i>Liepert et al.</i> (2000) Treatment-Induced Cortical Reorganization After Stroke in Humans. Stroke 31:1210-1216, 1211.	Thirteen patients “with chronic stroke (> 6 months) were studied”.

<i>Lotery et al.</i> (2000) Correctable visual impairment in stroke rehabilitation patients. <i>Age and Ageing</i> 29: 221-222.	“77 consecutive patients [were] admitted for rehabilitation after acute stroke” (with a mean interval of 15.5 days) and then “assessed within 2 weeks of admission . . .”
<i>Oddone et al.</i> (2000) Quality Enhancement Research Initiative in Stroke: Prevention, Treatment, and Rehabilitation. <i>Med. Care</i> 38:1092-1104.	Does not discuss specific studies.

These references disclose training protocols directed to a range of cognitive impairments, including locomotor function, speech and language, and visual memory. In every case for which there is relevant data, rehabilitation does not begin until several weeks following the acute phase of stroke, with most studies reporting a post-stroke interval of several months. Cognitive training in these studies, which also emphasize extensive screening and assessment phases, is active rehabilitation that occurs well beyond the acute phase of stroke.<sup>13</sup>

In sum, the Merck Manual, *Guideline*, the present application, and stroke the references incorporated therein all support the conclusion that cognitive training is a form of rehabilitation that necessarily occurs after the acute phase of stroke. Applicant respectfully asserts that that the Examiner’s reliance on the Merck Manual to argue that cognitive training can be administered during the acute phase is incorrect because it relies on a misplaced view of rehabilitation that is inapplicable to the instant claims.

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<sup>13</sup> To the extent that the Examiner has argued that activities such as “eating, dressing, toilet functions, other basic needs, passive exercises” etc. are forms of cognitive training, this argument is also inconsistent with a proper reading of the *Merck Manual*, the *Guideline*, and the instant specification.

**CONCLUSION**

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,

**/djpelto Reg. No. 33754/**

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